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Drive, Wilmington, DE 19808 (US). SELBY, Thomas, Paul [US/US]; 116 Hunter Court, Wilmington, DE 19808 (US). STEVENSON, Thomas, Martin [US/US]; 103 Iroquois Court, Newark, DE 19702 (US).

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(74) Agent: HEISER, David, E., E.I. du Pont de Nemours and Company, Legal Patent Records Center, 4417 Lancaster Pike, Wilmington, DE 19805 (US).

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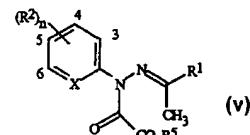
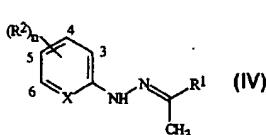
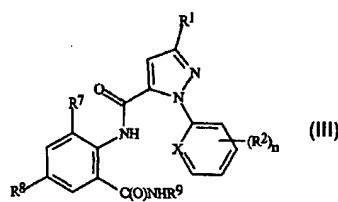
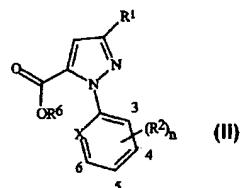
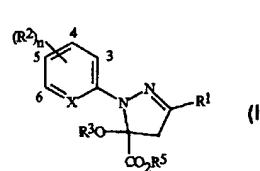
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(71) Applicant (for all designated States except US): E.I. DU PONT DE NEMOURS AND COMPANY [US/US]; 1007 Market Street, Wilmington, DE 19898 (US).

[Continued on next page]

(54) Title: NOVEL SUBSTITUTED 1H-DIHYDROPYRAZOLES, THEIR PREPARATION AND USE



(57) Abstract: This invention provides compounds of Formula (I), methods for their preparation and use for preparing compounds of Formula (II) wherein R₁, R₂, R₃, R₅, R₆, X and n are as defined in the disclosure. This invention also discloses preparation of compounds of Formula (III) wherein R₁, R₂, R₇, R₈, R₉ and n are as defined in the disclosure. This invention also pertains to certain compounds of Formula 4 and 6 used to prepare compounds of Formula (I), wherein R₁, R₂, R₅, X and n are as defined in the disclosure.

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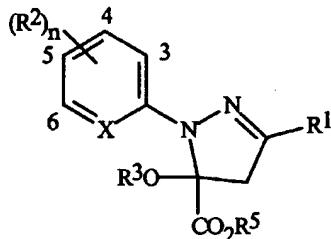
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TITLENOVEL SUBSTITUTED 1*H*-DIHYDROPYRAZOLES,
THEIR PREPARATION AND USEBACKGROUND OF THE INVENTION

5 This invention relates to novel carboxylic acid derivatives of 1-aryl-substituted dihydro-1*H*-pyrazoles and pyrazoles. These compounds are useful for preparation of certain anthranilic amide compounds that are of interest as insecticides (see e.g. PCT Publication WO 01/070671). *J. Med. Chem.* 2001, 44, 566-578 discloses a preparation of 1-(3-cyanophenyl)-3-methyl-1*H*-pyrazol-5-carboxylic acid and its use in preparing inhibitors of 10 blood coagulation factor Xa. The present invention provides technology useful for the successful and convenient preparation of 1-aryl-substituted dihydro-1*H*-pyrazoles and pyrazoles.

SUMMARY OF THE INVENTION

This invention provides compounds of Formula I



I

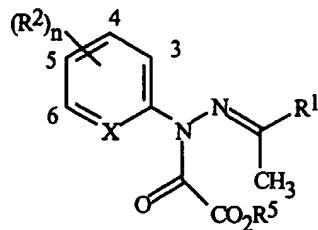
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wherein

20 R^1 is H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, C₁-C₆ haloalkyl, C₂-C₆ haloalkenyl, C₂-C₆ haloalkynyl or C₃-C₆ halocycloalkyl; each R^2 is independently C₁-C₄ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₆ cycloalkyl, C₁-C₄ haloalkyl, C₂-C₄ haloalkenyl, C₂-C₄ haloalkynyl, C₃-C₆ halocycloalkyl, halogen, CN, NO₂, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, C₁-C₄ alkylthio, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, C₁-C₄ alkylamino, C₂-C₈ dialkylamino, C₃-C₆ cycloalkylamino, C₃-C₆ (alkyl)cycloalkylamino, C₂-C₄ alkylcarbonyl, C₂-C₆ alkoxy carbonyl, C₂-C₆ alkylaminocarbonyl, C₃-C₈ dialkylaminocarbonyl or C₃-C₆ trialkylsilyl;

25 R^3 is H, C₁-C₄ alkyl, C₂-C₄ alkylcarbonyl or C₂-C₆ alkoxy carbonyl; X is N or CR⁴; R^4 is H or R²; R^5 is C₁-C₄ alkyl; and n is 0 to 3, provided when X is CH then n is at least 1.

This invention further provides a method of preparing a compound of Formula I. This method comprises (1) treating a compound of Formula 6



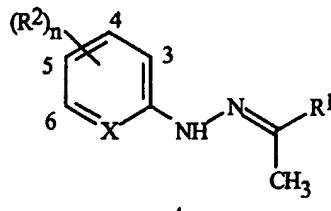
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(wherein X, R¹, R², R⁵ and n are defined as above for Formula I) with a base; and

5 when R³ is C₁-C₄ alkyl, C₂-C₄ alkylcarbonyl or C₂-C₆ alkoxy carbonyl, (2) reacting with an alkylating or acylating agent suitable for substituting an R³ for an alkoxide counterion to form a compound of Formula I.

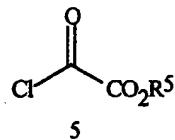
This invention also provides a compound of Formula 6, as well as a method for preparing a compound of Formula 6. This method comprises treating the compound of

10 Formula 4



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(wherein X, R¹, R² and n are defined as above for Formula I) with a compound of Formula 5

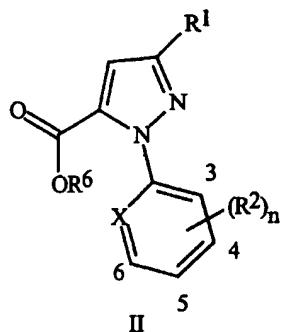


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wherein R⁵ is as defined above for Formula I, in the presence of base to form a compound of

15 Formula 6.

This invention further provides a method of preparing a compound of Formula II

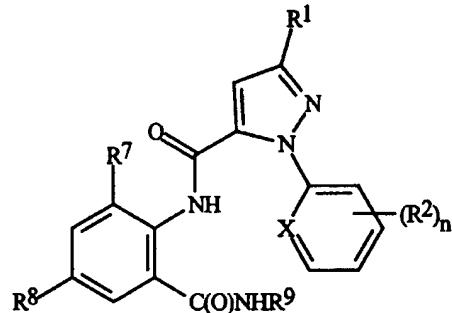


wherein X, R¹, R², and n are defined as above for Formula I, and R⁶ is R⁵ as defined above for Formula I or R⁵ is H. This method comprises (3) treating a compound of Formula I with acid; and when R⁶ is H (4) converting the product of (3) to form a compound of Formula II 5 wherein R⁶ is H.

This invention also provides compounds of Formula 4 wherein R¹ is CF₃; each R² is independently Cl or Br, and one R² is at the 3-position; X is N or CR⁴; R⁴ is H, Cl or Br; and n is 0, 1, 2 or 3; provided that (i) when X is CH or CCl then n is at least 1 and (ii) when X is CCl, an R² at the 3-position is Cl and an R² is at the 5-position is Cl then n is at least 3.

10 This invention also provides compounds of Formula II wherein R¹ is CF₃; each R² is independently Cl or Br, and one R² is at the 3-position; X is N or CR⁴; R⁴ is H or R²; R⁶ is H or C₁-C₄ alkyl; and n is 0, 1, 2 or 3, provided when X is CH then n is at least 1.

This invention also involves a method of preparing a compound of Formula III,



15 wherein X, R¹, R², and n are defined as above for Formula I; R⁷ is CH₃, Cl or Br; R⁸ is F, Cl, Br, I or CF₃; and R⁹ is C₁-C₄ alkyl, using a compound of Formula II wherein R⁶ is H. This method is characterized by preparing the compound of Formula II by the method as indicated above.

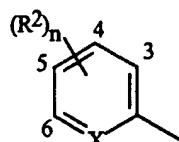
DETAILED DESCRIPTION OF THE INVENTION

20 In the above recitations, the term "alkyl", used either alone or in compound words such as "alkylthio" or "haloalkyl" includes straight-chain or branched alkyl, such as methyl, ethyl, n-propyl, i-propyl, or the different butyl, pentyl or hexyl isomers. "Alkenyl" can

include straight-chain or branched alkenes such as 1-propenyl, 2-propenyl, and the different butenyl, pentenyl and hexenyl isomers. "Alkenyl" also includes polyenes such as 1,2-propadienyl and 2,4-hexadienyl. "Alkynyl" includes straight-chain or branched alkynes such as 1-propynyl, 2-propynyl and the different butynyl, pentynyl and hexynyl isomers.

5 "Alkynyl" can also include moieties comprised of multiple triple bonds such as 2,5-hexadiynyl. "Alkoxy" includes, for example, methoxy, ethoxy, *n*-propyloxy, isopropyloxy and the different butoxy, pentoxy and hexyloxy isomers. "Alkylthio" includes branched or straight-chain alkylthio moieties such as methylthio, ethylthio, and the different propylthio, butylthio, pentylthio and hexylthio isomers. "Cycloalkyl" includes, for example, 10 cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. "Cycloalkylamino" means the amino nitrogen atom is attached to a cycloalkyl radical and a hydrogen atom and includes groups such as cyclopropylamino, cyclobutylamino, cyclopentylamino and cyclohexylamino. "(Alkyl)cycloalkylamino" means a cycloalkylamino group where the hydrogen atom is replaced by an alkyl radical; examples include groups such as (alkyl)cyclopropylamino, 15 (alkyl)cyclobutylamino, (alkyl)cyclopentylamino and (alkyl)cyclohexylamino. Preferably the alkyl in (alkyl)cycloalkylamino is C₁-C₄ alkyl, while the cycloalkyl in cycloalkylamino and (alkyl)cycloalkylamino is C₃-C₆ cycloalkyl.

The term "aryl" refers to an aromatic carbocyclic ring or ring system or a heteroaromatic ring or ring system, each ring or ring system optionally substituted. The term "aromatic ring system" denotes fully unsaturated carbocycles and heterocycles in which at least one ring of a polycyclic ring system is aromatic. Aromatic indicates that each of ring atoms is essentially in the same plane and has a *p*-orbital perpendicular to the ring plane, and in which (4*n* + 2) π electrons, when *n* is 0 or a positive integer, are associated with the ring to comply with Hückel's rule. The term "aromatic carbocyclic ring system" includes fully aromatic carbocycles and carbocycles in which at least one ring of a polycyclic ring system is aromatic (e. g. phenyl and naphthyl). The term "heteroaromatic ring or ring system" includes fully aromatic heterocycles and heterocycles in which at least one ring of a polycyclic ring system is aromatic and in which at least one ring atom is not carbon and can contain 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, 20 oxygen and sulfur, provided that each heteroaromatic ring contains no more than 4 nitrogens, no more than 2 oxygens and no more than 2 sulfurs (where aromatic indicates that the Hückel rule is satisfied). The heterocyclic ring systems can be attached through any available carbon or nitrogen by replacement of hydrogen on said carbon or nitrogen. More specifically, the term "aryl" refers to the moiety



wherein R², X and n are defined as above and the numerals 3 through 6 indicate respectively the 3-position through the 6-position for substituents on the moiety.

The term "halogen", either alone or in compound words such as "haloalkyl", includes fluorine, chlorine, bromine or iodine. Further, when used in compound words such as

5 "haloalkyl", said alkyl may be partially or fully substituted with halogen atoms which may be the same or different. Examples of "haloalkyl" include F₃C, ClCH₂, CF₃CH₂ and CF₃CCl₂. The terms "haloalkenyl", "haloalkynyl", "haloalkoxy", and the like, are defined analogously to the term "haloalkyl". Examples of "haloalkenyl" include (Cl)₂C=CHCH₂ and CF₃CH₂CH=CHCH₂. Examples of "haloalkynyl" include HC≡CCHCl, CF₃C≡C, 10 CCl₃C≡C and FCH₂C≡CCH₂. Examples of "haloalkoxy" include CF₃O, CCl₃CH₂O, HCF₂CH₂CH₂O and CF₃CH₂O.

15 Examples of "alkylcarbonyl" include C(O)CH₃, C(O)CH₂CH₂CH₃ and C(O)CH(CH₃)₂. Examples of "alkoxycarbonyl" include CH₃OC(=O), CH₃CH₂OC(=O), CH₃CH₂CH₂OC(=O), (CH₃)₂CHOC(=O) and the different butoxy- or pentoxy carbonyl isomers. The terms "alkylaminocarbonyl" and "dialkylaminocarbonyl" include, for 20 example, CH₃NHC(=O), CH₃CH₂NHC(=O) and (CH₃)₂NC(=O).

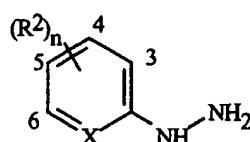
The total number of carbon atoms in a substituent group is indicated by the "C_i-C_j" prefix where i and j are numbers from 1 to 8. For example, C₁-C₃ alkylsulfonyl designates methylsulfonyl through propylsulfonyl. In the above recitations, when a compound of 25 Formula I contains a heteroaromatic ring, all substituents are attached to this ring through any available carbon or nitrogen by replacement of a hydrogen on said carbon or nitrogen.

When a group contains a substituent which can be hydrogen, for example R¹, then, when this substituent is taken as hydrogen, it is recognized that this is equivalent to said group being unsubstituted.

25 Compounds of this invention can exist as one or more stereoisomers. The various stereoisomers include enantiomers, diastereomers, atropisomers and geometric isomers. One skilled in the art will appreciate that one stereoisomer may be more active and/or may exhibit beneficial effects when enriched relative to the other stereoisomer(s) or when separated from the other stereoisomer(s). Additionally, the skilled artisan knows how to 30 separate, enrich, and/or to selectively prepare said stereoisomers. Accordingly, the compounds of the invention may be present as a mixture of stereoisomers, individual stereoisomers, or as an optically active form.

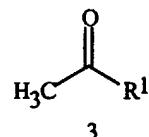
Compounds of Formula I and compounds of Formula II can be prepared by the stepwise process comprising:

35 (a) treating, optionally in the presence of acid, a compound of Formula 2

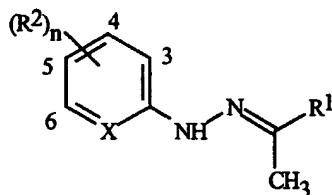


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(wherein X, R² and n are defined as above) with a compound of Formula 3



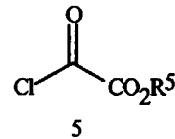
(wherein R¹ is defined as above) to form a compound of Formula 4



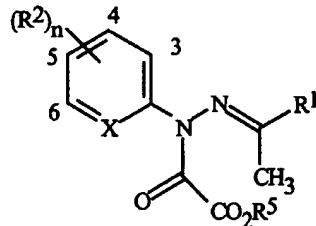
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(wherein X, R¹, R² and n are defined as above);

(b) treating said compound of Formula 4 with a compound of Formula 5



wherein R⁵ is C₁-C₄ alkyl, in the presence of base to form a compound of Formula 6



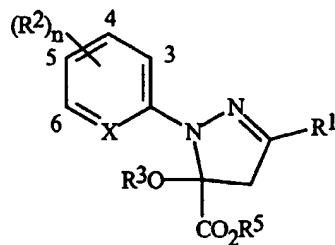
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(wherein X, R¹, R², R⁵ and n are defined as above);

(1) treating said compound of Formula 6 with a base to form a compound of Formula I wherein R³ is H; and (2) when R³ is C₁-C₄ alkyl, C₂-C₄ alkylcarbonyl or C₂-C₆ alkoxy carbonyl, reacting with an alkylating or acylating agent to form a compound of

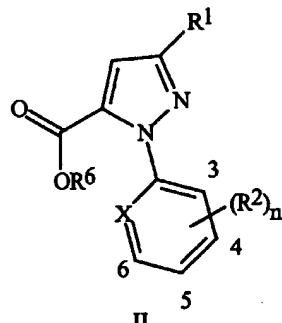
15 Formula I



I

(wherein X, R¹, R², R⁵ and n are defined as above);

(3) treating a compound of Formula I with acid; and when R⁶ is H (4) converting the product of (3) to form a compound of Formula II wherein R⁶ is H.



II

5

wherein X, R¹, R², R⁵ and n are defined as above.

Preferred 1. Compounds of Formula I wherein R¹ is H, C₁-C₄ alkyl or C₁-C₄ haloalkyl; and each R² is independently C₁-C₄ alkyl, C₁-C₄ haloalkyl, halogen or CN.

Preferred 2. Compounds of Formula I wherein

10 R¹ is H, C₁-C₄ alkyl or C₁-C₄ haloalkyl;
X is N; and
n is 0.

Preferred 3. Compounds of Preferred 1 wherein

15 R¹ is CF₃;
each R² is independently Cl or Br, and one R² is at the 3-position;
R³ is H; and
R⁴ is H, Cl or Br.

Preferred 4. Compounds of Preferred 1 wherein

20 R¹ is CF₃;
one R² is at the 4-position and is CN, and if an R² is present at the 5-position,
it is F;
R³ is H; and
X is CH.

Preferred 5. Compounds of Preferred 1 wherein X is N.

Of note are the compounds of Formula I (including, but not limited to the compounds of Preferred 1, Preferred 3, Preferred 4 and Preferred 5) wherein n is from 1 to 3.

Preferred 6. The method of preparing a compound of Formula I from a compound of Formula 6 wherein step (1) comprises treating the compound of Formula 6 with 5 a quaternary ammonium fluoride salt.

Preferred 7. The method of preparing a compound of Formula I from a compound of Formula 6 wherein R¹ is H, C₁-C₄ alkyl or C₁-C₄ haloalkyl; and each R² is independently C₁-C₄ alkyl, C₁-C₄ haloalkyl, halogen or CN.

Preferred 8. The method of Preferred 7 wherein R¹ is CF₃; and each R² is independently 10 Cl or Br, and one R² is at the 3-position.

Preferred 9. The method of Preferred 7 wherein
R¹ is CF₃;
one R² is at the 4-position and is CN, and if an R² is present at the 5-position, 15 it is F;
R³ is H; and
X is CH.

Preferred 10. The method of preparing a compound of Formula I from a compound of Formula 6 wherein X is N.

Of note are methods of preparing a compound of Formula I from a compound of 20 Formula 6 (including, but not limited to the methods of Preferred 6, Preferred 7, Preferred 8, Preferred 9 and Preferred 10) wherein n is from 1 to 3.

Preferred 11. Compounds of Formula 6 wherein R¹ is H, C₁-C₄ alkyl or C₁-C₄ haloalkyl; and each R² is independently C₁-C₄ alkyl, C₁-C₄ haloalkyl, halogen or CN.

Preferred 12. Compounds of Formula 6 wherein
R¹ is H, C₁-C₄ alkyl or C₁-C₄ haloalkyl;
X is N; and
n is 0.

Preferred 13. Compounds of Preferred 11 wherein
R¹ is CF₃;
each R² is independently Cl or Br, and one R² is at the 3-position;
X is N or CR⁴; and
R⁴ is H, Cl or Br.

Preferred 14. Compounds of Preferred 11 wherein R¹ is CF₃; one R² is at the 35 4-position and is CN, and if an R² is present at the 5-position, it is F; and X is CH.

Preferred 15. Compounds of Preferred 11 wherein X is N.

Preferred 16. Compounds of Formula II wherein X is N.

Of note are compounds of Formula 6 (including, but not limited to the compounds of Preferred 11, Preferred 13, Preferred 14, and Preferred 15) wherein n is from 1 to 3.

The 3-, 4- or 5-positions are identified by the corresponding numerals shown in the aryl moiety included in Formula I, Formula II, Formula 4 and Formula 6 above.

5 Of note are compounds of Formula 4 wherein R¹ is CF₃; each R² is independently Cl or Br, and one R² is at the 3-position; X is N or CR⁴; R⁴ is H, Cl or Br; and n is 1, 2 or 3.

Of note are compounds of Formula 4 wherein X is N.

Of note are compounds of Formula II wherein n is 1, 2 or 3.

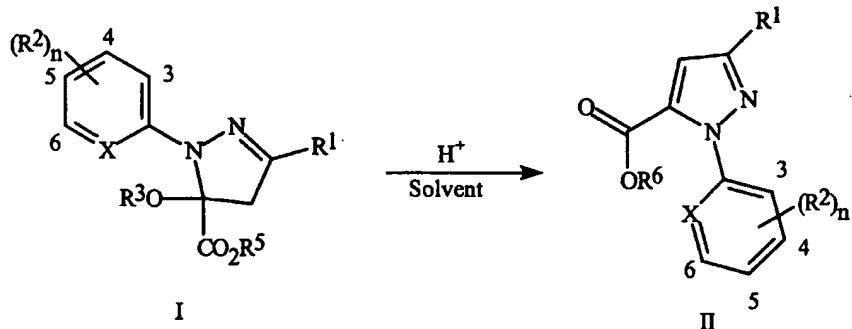
10 Of note are compounds of Formula II wherein R¹ is CF₃; each R² is independently Cl or Br, and one R² is at the 3-position; X is N or CR⁴; R⁴ is H or R²; R⁶ is H or C₁-C₄ alkyl; and n is 1, 2 or 3.

Of note are compounds of Formula II wherein when R¹ is CF₃, n is 1, and R² selected from Cl or Br is at the 3-position; then X is N. Examples include those where n is from 1 to 3.

15 Of note are compounds of Formula II wherein when R¹ is CF₃, n is 1, and R² selected from Cl or Br is at the 3-position; then X is CR⁴. Examples include those where n is from 1 to 3.

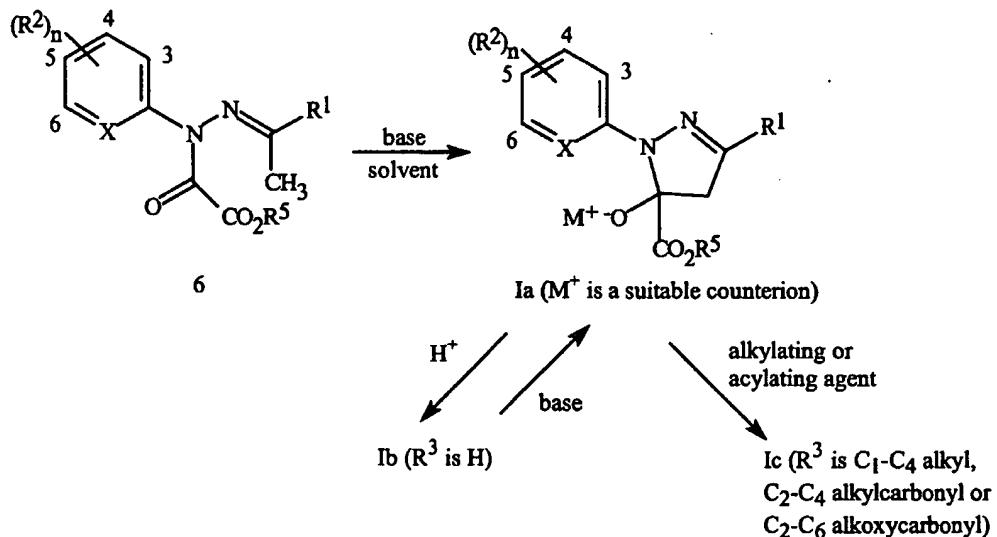
Preferred methods of preparing compounds I, II and 6 comprise the preferred compounds above.

20 As shown in Scheme 1, compounds of Formula II can be prepared from compounds of Formula I by treatment with a catalytic amount of a suitable acid. The catalytic acid can be, for example, sulfuric acid. The reaction is generally conducted using an organic solvent. As one skilled in the art will realize, dehydration reactions can be conducted in a wide variety of solvents in a temperature range generally between about 0 and 200 °C, more 25 preferably between about 0 and 100 °C. For the dehydration in the method of Scheme 1, a solvent comprising acetic acid and temperatures of about 65 °C are preferred. Compounds of Formula I wherein R³ is H are preferred for this transformation. Compounds of Formula II (R⁶ is C₁-C₄ alkyl) can be converted to compounds of Formula II (R⁶ is H) by numerous methods including nucleophilic cleavage under anhydrous conditions or hydrolytic methods 30 involving the use of either acids or bases (see T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, 2nd ed., John Wiley & Sons, Inc., New York, 1991, pp. 224-269 for a review of methods). Base-catalyzed hydrolytic methods are preferred. Suitable bases include alkali metal (such as lithium, sodium or potassium) hydroxides. For example, the ester can be dissolved in a mixture of water and alcohol such as ethanol. Upon treatment 35 with sodium hydroxide or potassium hydroxide, the ester is saponified to provide the sodium salt of the carboxylic acid. Acidification with a strong acid, such as hydrochloric acid or sulfuric acid, yields the carboxylic acid. The carboxylic acid can be isolated by methods known to those skilled in the art, including crystallization, extraction and distillation.

Scheme 1

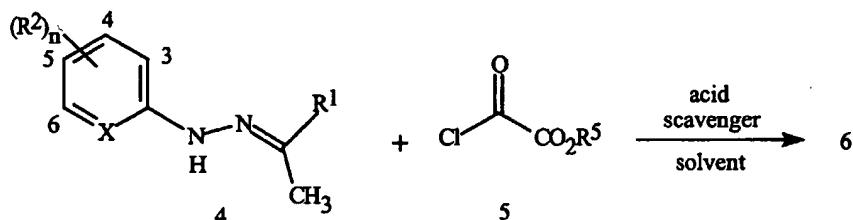
As illustrated in Scheme 2, compounds of Formula I can be prepared from compounds of Formula 6 by treatment with a suitable base in a suitable organic solvent. Examples of suitable bases include (but are not limited to) sodium hydride, potassium *t*-butoxide, dimsyl sodium ($\text{CH}_3\text{S}(\text{O})\text{CH}_2^- \text{Na}^+$), alkali metal (such as lithium, sodium or potassium) carbonates or hydroxides, tetraalkyl (such as methyl, ethyl or butyl)ammonium fluorides or hydroxides, or 2-*tert*-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphonine. Examples of suitable organic solvents include (but are not limited to) acetone, acetonitrile, tetrahydrofuran, dichloromethane, dimethylsulfoxide, and *N,N*-dimethylformamide. The cyclization reaction is usually conducted in a temperature range from about 0 to 120 °C. The effects of solvent, base, temperature and addition time are all interdependent, and choice of reaction conditions is important to minimize the formation of byproducts. A preferred base is tetrabutylammonium fluoride. The intermediate formed in the reaction, Formula Ia wherein M^+ is a suitable counterion derived from the base, is then protonated by a suitable acid (for example, acetic acid) to give compounds of Formula Ib wherein R^3 is H. As one skilled in the art will know, intermediates such as Ia may be alkylated or acylated by the addition of a suitable alkylating or acylating agent to give compounds of Formula Ic wherein R^3 is $\text{C}_1\text{-C}_4$ alkyl, $\text{C}_2\text{-C}_4$ alkylcarbonyl or $\text{C}_2\text{-C}_6$ alkoxy carbonyl. Alternatively, compounds of Formula Ic can be prepared from compounds of Formula Ib in a separate chemical step using a suitable base and alkylating or acylating agent. Suitable alkylating agents include $\text{C}_1\text{-C}_4$ alkyl halides, sulfates and sulfonates; suitable acylating agents include acid chlorides or anhydrides and chloroformates. In any case, when using Ia or Ib, an alkylating or acylating agent suitable for substituting an R^3 for an alkoxide counterion is used.

Scheme 2



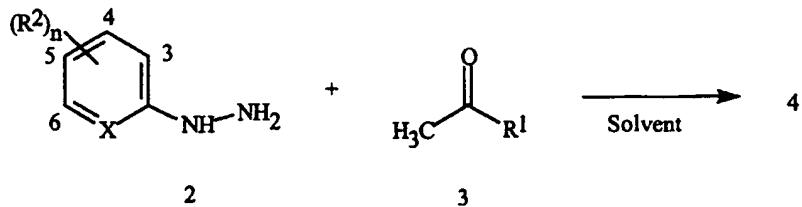
Compounds of Formula 6 can be prepared by treatment of compounds of Formula 4 with compounds of Formula 5 in a suitable organic solvent in the presence of an acid scavenger such as triethylamine. Examples of suitable organic solvents include (but are not limited to) dichloromethane and tetrahydrofuran. The reaction is usually conducted at a temperature between about 0 and 100 °C. Scheme 3 illustrates this transformation.

Scheme 3



10 As illustrated by Scheme 4, the hydrazone compound of Formula 4 can be prepared from hydrazine compound of Formula 2 by treatment with a compound of Formula 3 in a solvent such as water, methanol or acetic acid. One skilled in the art will recognize that this reaction may require catalysis by an optional acid and may also require elevated temperatures depending on the molecular substitution pattern of the hydrazone of Formula 4.

Scheme 4



Without further elaboration, it is believed that one skilled in the art using the preceding description can utilize the present invention to its fullest extent. The following Examples are, therefore, to be construed as merely illustrative, and not limiting of the disclosure in any way whatsoever. The starting material for the following Examples may not have necessarily 5 been prepared by a particular preparative run whose procedure is described in other Examples. Percentages are by weight except for chromatographic solvent mixtures or where otherwise indicated. Parts and percentages for chromatographic solvent mixtures are by volume unless otherwise indicated. ^1H NMR spectra are reported in ppm downfield from tetramethylsilane; "s" means singlet, "d" means doublet, "t" means triplet, "q" means 10 quartet, "m" means multiplet, "dd" means doublet of doublets, "dt" means doublet of triplets, and "br s" means broad singlet.

EXAMPLE 1

Preparation of 3-Chloro-2(1*H*)-pyridinone (2,2,2-trifluoro-1-methylethylidene)hydrazone

1,1,1-Trifluoroacetone (7.80 g, 69.6 mmol) was added to (3-chloro-pyridin-2-yl)-15 hydrazine (alternatively named (3-chloro-pyridin-2-yl)-hydrazine) (10 g, 69.7 mmol) at 20-25 °C. After the addition was complete, the mixture was stirred for about 10 minutes. The solvent was removed under reduced pressure, and the mixture was partitioned between 20 ethyl acetate (100 mL) and saturated sodium carbonate solution (100 mL). The organic layer was dried and evaporated. Chromatography on silica gel (eluted with ethyl acetate) gave the product as an off-white solid (11 g, 66% yield), m.p. 64-64.5 °C (after crystallization from ethyl acetate/hexanes).

IR (nujol) ν 1629, 1590, 1518, 1403, 1365, 1309, 1240, 1196, 1158, 1100, 1032, 992, 800 cm^{-1} .
1*H* NMR (CDCl_3) δ 2.12 (s, 3H), 6.91-6.86 (m, 1H), 7.64-7.61 (m, 1H), 8.33-8.32 (m, 2H).
25 MS m/z 237 (M^+).

EXAMPLE 2Preparation of Ethyl hydrogen ethanedioate (3-chloro-2-pyridinyl) (2,2,2-trifluoro-1-methylethylidene)hydrazide

Triethylamine (20.81 g, 0.206 mol) was added to 3-chloro-2(1*H*)-pyridinone (2,2,2-trifluoro-1-methylethylidene)hydrazone (i.e. the product of Example 1) (32.63 g, 0.137 mol) in dichloromethane (68 mL) at 0 °C. Ethyl chlorooxoacetate (18.75 g, 0.137 mol) in dichloromethane (69 mL) was added dropwise to the mixture at 0 °C. The mixture was allowed to warm to 25 °C over about 2 hours. The mixture was cooled to 0 °C and a further portion of ethyl chlorooxoacetate (3.75 g, 27.47 mmol) in dichloromethane (14 mL) was added dropwise. After about an additional 1 hour, the mixture was diluted with dichloromethane (about 450 mL), and the mixture was washed with water (2 x 150 mL). The organic layer was dried and evaporated. Chromatography on silica gel (eluted with 1:1 ethyl acetate–hexanes) gave the product as a solid (42.06 g, 90% yield), m.p. 73.0–73.5 °C (after crystallization from ethyl acetate/hexanes).

IR (nujol) ν 1751, 1720, 1664, 1572, 1417, 1361, 1330, 1202, 1214, 1184, 1137, 1110, 1004, 1043, 1013, 942, 807, 836 cm^{-1} .

^1H NMR (DMSO-*d*₆, 115 °C) δ 1.19 (t, 3H), 1.72 (br s, 3H), 4.25 (q, 2H), 7.65 (dd, *J* = 8.3, 4.7 Hz, 1H), 8.20 (dd, *J* = 7.6, 1.5 Hz, 1H), 8.55 (d, *J* = 3.6 Hz, 1H).

MS *m/z* 337 (M⁺).

EXAMPLE 3Preparation of Ethyl 1-(3-chloro-2-pyridinyl)-4,5-dihydro-5-hydroxy-3-(trifluoromethyl)-1*H*-pyrazole-5-carboxylate

Ethyl hydrogen ethanedioate (3-chloro-2-pyridinyl) (2,2,2-trifluoro-1-methylethylidene)hydrazide (i.e. the product of Example 2) (5 g, 14.8 mmol) in dimethyl sulfoxide (25 mL) was added to tetrabutylammonium fluoride hydrate (10 g) in dimethyl sulfoxide (25 mL) over 8 hours. When the addition was complete, the mixture was poured into a mixture of acetic acid (3.25 g) and water (25 mL). After stirring at 25 °C overnight, the mixture was then extracted with toluene (4 x 25 mL), and the combined toluene extracts were washed with water (50 mL), dried and evaporated to give a solid. Chromatography on silica gel (eluted with 1:2 ethyl acetate–hexanes) gave the product as a solid (2.91 g, 50% yield, containing about 5% of 3-chloro-2(1*H*)-pyridinone (2,2,2-trifluoro-1-methylethylidene)hydrazone), m.p. 78–78.5 °C (after recrystallization from ethyl acetate/hexanes).

IR (nujol) ν 3403, 1726, 1618, 1582, 1407, 1320, 1293, 1260, 1217, 1187, 1150, 1122, 1100, 1067, 1013, 873, 829 cm^{-1} .

^1H NMR (CDCl₃) δ 1.19 (s, 3H), 3.20 (1/2 of ABZ pattern, *J* = 18 Hz, 1H), 3.42 (1/2 of ABZ pattern, *J* = 18 Hz, 1H), 4.24 (q, 2H), 6.94 (dd, *J* = 7.9, 4.9 Hz, 1H), 7.74 (dd, *J* = 7.7, 1.5 Hz, 1H), 8.03 (dd, *J* = 4.7, 1.5 Hz, 1H).

MS *m/z* 319 (M⁺).

EXAMPLE 4

Preparation of Ethyl 1-(3-chloro-2-pyridinyl)-3-(trifluoromethyl)-1*H*-pyrazole-5-carboxylate

Sulfuric acid (concentrated, 2 drops) was added to ethyl 1-(3-chloro-2-pyridinyl)-4,5-dihydro-5-hydroxy-3-(trifluoromethyl)-1*H*-pyrazole-5-carboxylate (i.e. the product of Example 3) (1 g, 2.96 mmol) in acetic acid (10 mL) and the mixture was warmed to 65 °C for about 1 hour. The mixture was allowed to cool to 25 °C and most of the acetic acid was removed under reduced pressure. The mixture was partitioned between saturated aqueous sodium carbonate solution (100 mL) and ethyl acetate (100 mL). The aqueous layer was further extracted with ethyl acetate (100 mL). The combined organic extracts were dried and evaporated to give the product as an oil (0.66 g, 77% yield).

IR (neat) ν 3147, 2986, 1734, 1577, 1547, 1466, 1420, 1367, 1277, 1236, 1135, 1082, 1031, 973, 842, 802 cm⁻¹.

¹H NMR (CDCl₃) δ 1.23 (t, 3H), 4.25 (q, 2H), 7.21 (s, 1H), 7.48 (dd, *J* = 8.1, 4.7 Hz, 1H), 7.94 (dd, *J* = 6.6, 2 Hz, 1H), 8.53 (dd, *J* = 4.7, 1.5 Hz, 1H).

MS *m/z* 319 (M⁺).

EXAMPLE 5

Preparation of 1-(3-chloro-2-pyridinyl)-3-(trifluoromethyl)-1*H*-pyrazole-5-carboxylic acid

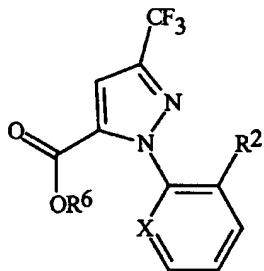
Potassium hydroxide (0.5 g, 85%, 2.28 mmol) in water (1 mL) was added to ethyl 1-(3-chloro-2-pyridinyl)-3-(trifluoromethyl)-1*H*-pyrazole-5-carboxylate (i.e. the product of Example 4) (0.66 g, 2.07 mmol) in ethanol (3 mL). After about 30 minutes, the solvent was removed under reduced pressure, and the mixture was dissolved in water (40 mL). The solution was washed with ethyl acetate (20 mL). The aqueous layer was acidified with concentrated hydrochloric acid and was extracted with ethyl acetate (3 x 20 mL). The combined extracts were dried and evaporated to give the product as a solid (0.53 g, 93% yield), m.p. 178–179 °C (after crystallization from hexanes–ethyl acetate).

IR (nujol) ν 1711, 1586, 1565, 1550, 1440, 1425, 1292, 1247, 1219, 1170, 1135, 1087, 1059, 1031, 972, 843, 816 cm⁻¹.

¹H NMR (DMSO-*d*₆) δ 7.61 (s, 1H), 7.77 (m, 1H), 8.30 (d, 1H), 8.60 (s, 1H).

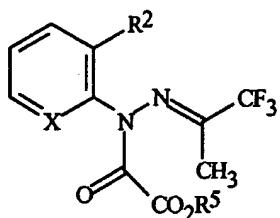
By the procedures described herein together with methods known in the art, the following compounds of Tables 1 to 5 can be prepared. The following abbreviations are used in the Tables: *t* is tertiary, *s* is secondary, *n* is normal, *i* is iso, Me is methyl, Et is ethyl, Pr is propyl, *i*-Pr is isopropyl and *t*-Bu is tertiary butyl.

TABLE 1



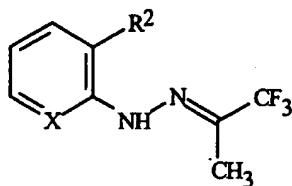
X is N				X is CH				X is CCl				X is CBr			
<u>R</u> ²	<u>R</u> ⁶														
Cl	H	Br	H												
Cl	Me	Br	Me												
Cl	Et	Br	Et												
Cl	<i>n</i> -Pr	Br	<i>n</i> -Pr	Cl	<i>n</i> -Pr	Br	<i>n</i> -Pr	Cl	<i>n</i> -Pr	Br	<i>n</i> -Pr	Cl	<i>n</i> -Pr	Br	<i>n</i> -Pr
Cl	<i>i</i> -Pr	Br	<i>i</i> -Pr	Cl	<i>i</i> -Pr	Br	<i>i</i> -Pr	Cl	<i>i</i> -Pr	Br	<i>i</i> -Pr	Cl	<i>i</i> -Pr	Br	<i>i</i> -Pr
Cl	<i>n</i> -Bu	Br	<i>n</i> -Bu	Cl	<i>n</i> -Bu	Br	<i>n</i> -Bu	Cl	<i>n</i> -Bu	Br	<i>n</i> -Bu	Cl	<i>n</i> -Bu	Br	<i>n</i> -Bu
Cl	<i>i</i> -Bu	Br	<i>i</i> -Bu	Cl	<i>i</i> -Bu	Br	<i>i</i> -Bu	Cl	<i>i</i> -Bu	Br	<i>i</i> -Bu	Cl	<i>i</i> -Bu	Br	<i>i</i> -Bu
Cl	<i>s</i> -Bu	Br	<i>s</i> -Bu	Cl	<i>s</i> -Bu	Br	<i>s</i> -Bu	Cl	<i>s</i> -Bu	Br	<i>s</i> -Bu	Cl	<i>s</i> -Bu	Br	<i>s</i> -Bu
Cl	<i>t</i> -Bu	Br	<i>t</i> -Bu	Cl	<i>t</i> -Bu	Br	<i>t</i> -Bu	Cl	<i>t</i> -Bu	Br	<i>t</i> -Bu	Cl	<i>t</i> -Bu	Br	<i>t</i> -Bu

TABLE 2



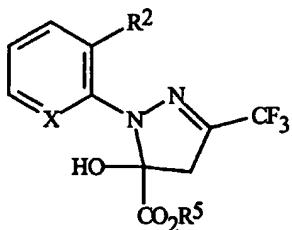
X is N				X is CH				X is CCl				X is CBr			
<u>R</u> ²	<u>R</u> ⁵														
Cl	Me	Br	Me												
Cl	Et	Br	Et												
Cl	<i>n</i> -Pr	Br	<i>n</i> -Pr	Cl	<i>n</i> -Pr	Br	<i>n</i> -Pr	Cl	<i>n</i> -Pr	Br	<i>n</i> -Pr	Cl	<i>n</i> -Pr	Br	<i>n</i> -Pr
Cl	<i>i</i> -Pr	Br	<i>i</i> -Pr	Cl	<i>i</i> -Pr	Br	<i>i</i> -Pr	Cl	<i>i</i> -Pr	Br	<i>i</i> -Pr	Cl	<i>i</i> -Pr	Br	<i>i</i> -Pr
Cl	<i>n</i> -Bu	Br	<i>n</i> -Bu	Cl	<i>n</i> -Bu	Br	<i>n</i> -Bu	Cl	<i>n</i> -Bu	Br	<i>n</i> -Bu	Cl	<i>n</i> -Bu	Br	<i>n</i> -Bu
Cl	<i>i</i> -Bu	Br	<i>i</i> -Bu	Cl	<i>i</i> -Bu	Br	<i>i</i> -Bu	Cl	<i>i</i> -Bu	Br	<i>i</i> -Bu	Cl	<i>i</i> -Bu	Br	<i>i</i> -Bu
Cl	<i>s</i> -Bu	Br	<i>s</i> -Bu	Cl	<i>s</i> -Bu	Br	<i>s</i> -Bu	Cl	<i>s</i> -Bu	Br	<i>s</i> -Bu	Cl	<i>s</i> -Bu	Br	<i>s</i> -Bu
Cl	<i>t</i> -Bu	Br	<i>t</i> -Bu	Cl	<i>t</i> -Bu	Br	<i>t</i> -Bu	Cl	<i>t</i> -Bu	Br	<i>t</i> -Bu	Cl	<i>t</i> -Bu	Br	<i>t</i> -Bu

TABLE 3



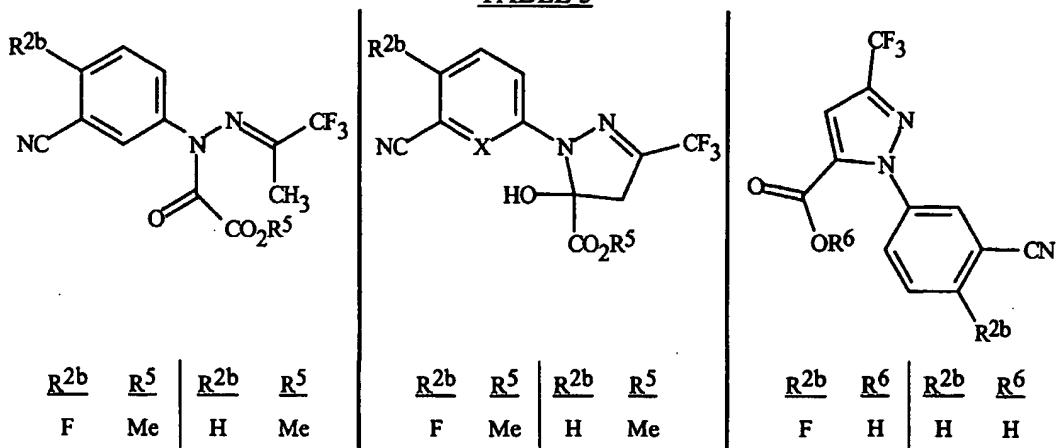
<u>X is N</u>	<u>X is CH</u>	<u>X is CCl</u>	<u>X is CBr</u>
<u>R²</u>	<u>R²</u>	<u>R²</u>	<u>R²</u>
Cl	Br	Cl	Br

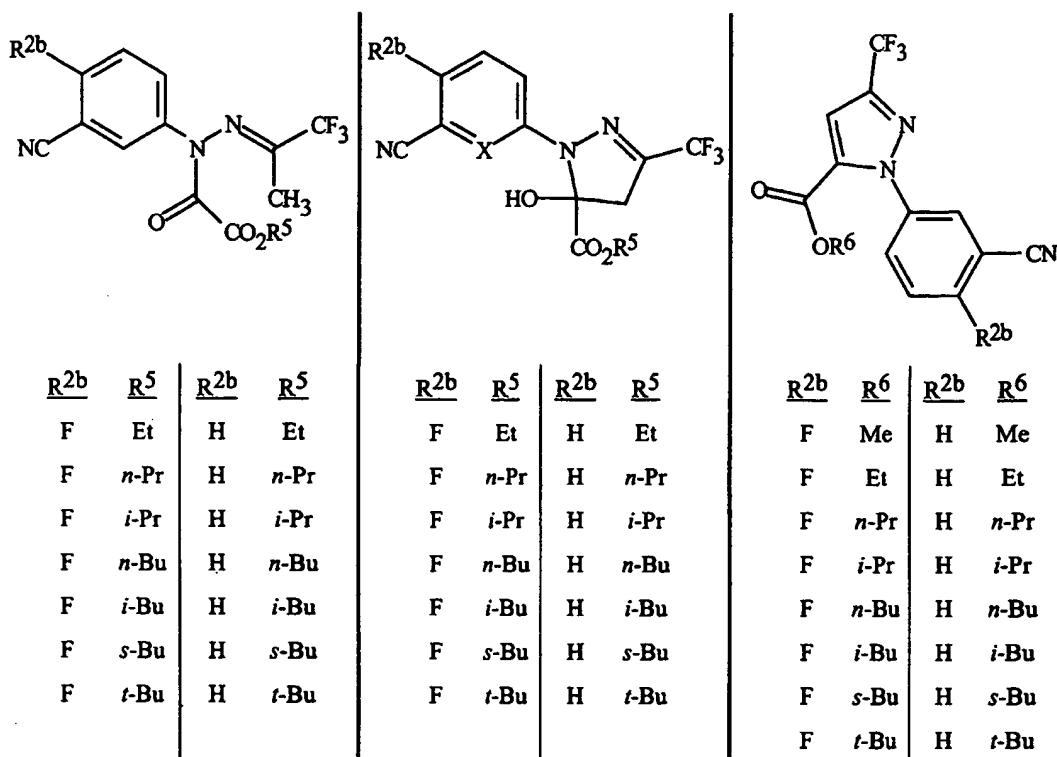
TABLE 4



X is N				X is CH				X is CCl				X is CBr			
<u>R</u> ²	<u>R</u> ⁵														
Cl	Me	Br	Me												
Cl	Et	Br	Et												
Cl	<i>n</i> -Pr	Br	<i>n</i> -Pr	Cl	<i>n</i> -Pr	Br	<i>n</i> -Pr	Cl	<i>n</i> -Pr	Br	<i>n</i> -Pr	Cl	<i>n</i> -Pr	Br	<i>n</i> -Pr
Cl	<i>i</i> -Pr	Br	<i>i</i> -Pr	Cl	<i>i</i> -Pr	Br	<i>i</i> -Pr	Cl	<i>i</i> -Pr	Br	<i>i</i> -Pr	Cl	<i>i</i> -Pr	Br	<i>i</i> -Pr
Cl	<i>n</i> -Bu	Br	<i>n</i> -Bu	Cl	<i>n</i> -Bu	Br	<i>n</i> -Bu	Cl	<i>n</i> -Bu	Br	<i>n</i> -Bu	Cl	<i>n</i> -Bu	Br	<i>n</i> -Bu
Cl	<i>i</i> -Bu	Br	<i>i</i> -Bu	Cl	<i>i</i> -Bu	Br	<i>i</i> -Bu	Cl	<i>i</i> -Bu	Br	<i>i</i> -Bu	Cl	<i>i</i> -Bu	Br	<i>i</i> -Bu
Cl	<i>s</i> -Bu	Br	<i>s</i> -Bu	Cl	<i>s</i> -Bu	Br	<i>s</i> -Bu	Cl	<i>s</i> -Bu	Br	<i>s</i> -Bu	Cl	<i>s</i> -Bu	Br	<i>s</i> -Bu
Cl	<i>t</i> -Bu	Br	<i>t</i> -Bu	Cl	<i>t</i> -Bu	Br	<i>t</i> -Bu	Cl	<i>t</i> -Bu	Br	<i>t</i> -Bu	Cl	<i>t</i> -Bu	Br	<i>t</i> -Bu

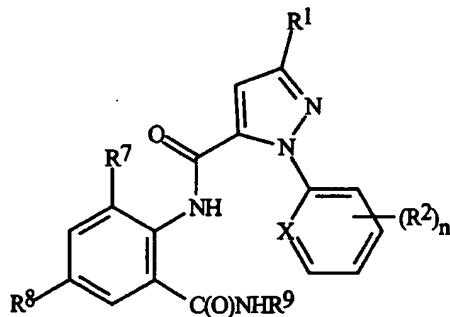
TABLE 5





Utility

The compounds of Formulae I, II, 4 and 6 are useful as synthetic intermediates for preparing a compound of Formula III



III

5 wherein X, R¹, R² and n are defined as above; R⁷ is CH₃, Cl or Br; R⁸ is F, Cl, Br, I or CF₃; and R⁹ is C₁-C₄ alkyl.

Compounds of Formula III are useful as insecticides.

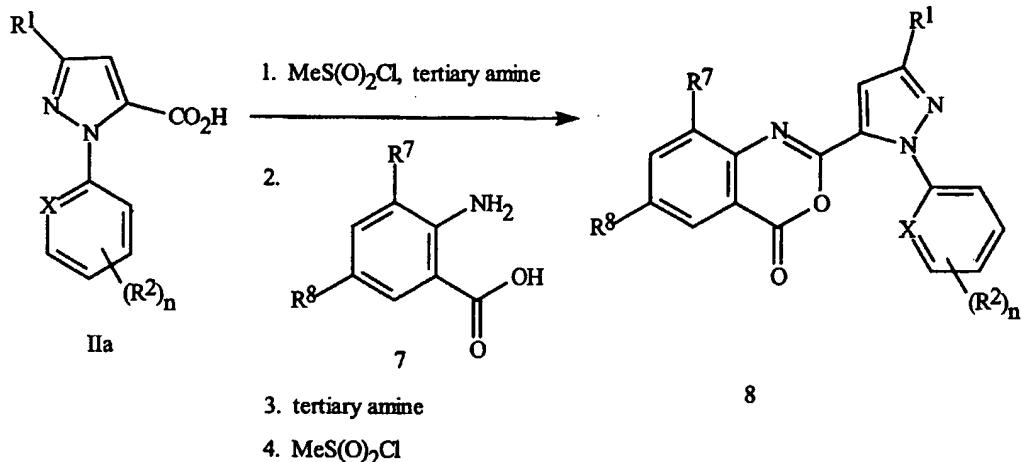
Compounds of Formula III can be prepared from compounds of Formula II (and in turn from compounds of Formula 4, 6 and I) by the processes outlined in Schemes 5-7.

10 Coupling of a pyrazolecarboxylic acid of Formula IIa (a compound of Formula II wherein R⁶ is H) with an anthranilic acid of Formula 7 provides a benzoxazinone of Formula 8. In Scheme 5, a benzoxazinone of Formula 8 is prepared directly via sequential addition of

methanesulfonyl chloride in the presence of a tertiary amine such as triethylamine or pyridine to a pyrazolecarboxylic acid of Formula IIa, followed by the addition of an anthranilic acid of Formula 7, followed by a second addition of tertiary amine and methanesulfonyl chloride. This procedure generally affords good yields of the

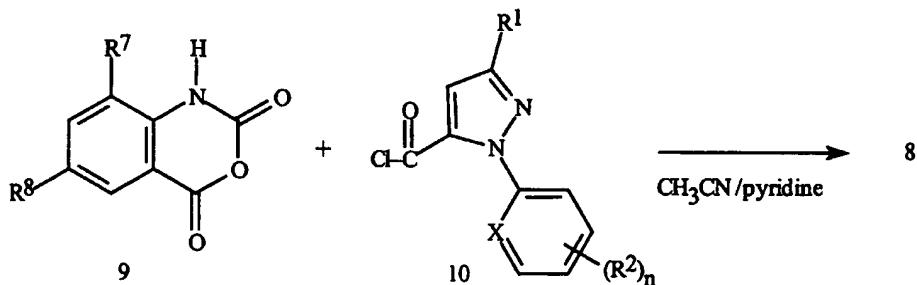
5 benzoxazinone.

Scheme 5



Scheme 6 depicts an alternate preparation of benzoxazinones of Formula 8 involving coupling of a pyrazole acid chloride of Formula 10 with an isatoic anhydride of Formula 9 to provide the Formula 8 benzoxazinone directly.

Scheme 6

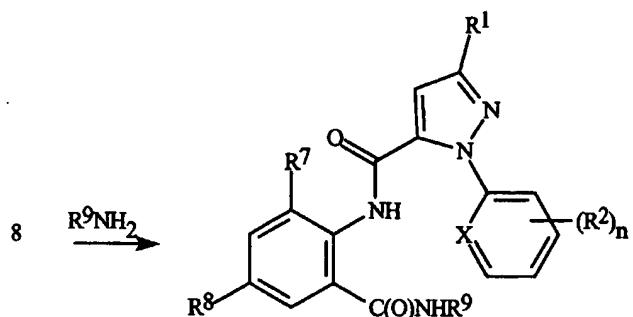


Solvents such as pyridine or pyridine/acetonitrile are suitable for this reaction. The acid chlorides of Formula 10 are available from the corresponding acids of Formula IIa by known procedures such as chlorination with thionyl chloride or oxalyl chloride.

15 Compounds of Formula III can be prepared by the reaction of benzoxazinones of Formula 8 with C₁–C₄ alkyl amines as outlined in Scheme 7. The reaction can be run neat or in a variety of suitable solvents including tetrahydrofuran, diethyl ether, dichloromethane or chloroform with optimum temperatures ranging from room temperature to the reflux 20 temperature of the solvent. The general reaction of benzoxazinones with amines to produce anthranilamides is well documented in the chemical literature. For a review of

benzoxazinone chemistry see Jakobsen et al., *Biorganic and Medicinal Chemistry* 2000, 8, 2095–2103 and references cited within. See also Coppola, *J. Heterocyclic Chemistry* 1999, 36, 563–588.

Scheme 7



5

III

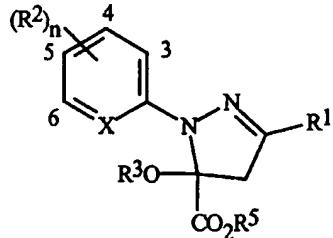
Of note are methods of preparing compounds of Formula III wherein n is 0.

Also of note are methods of preparing compounds of Formula III wherein n is from 1 to 3.

CLAIMS

What is claimed is:

1. A compound of Formula I



I

5 wherein

R¹ is H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, C₁-C₆ haloalkyl, C₂-C₆ haloalkenyl, C₂-C₆ haloalkynyl or C₃-C₆ halocycloalkyl; each R² is independently C₁-C₄ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₆ cycloalkyl, C₁-C₄ haloalkyl, C₂-C₄ haloalkenyl, C₂-C₄ haloalkynyl, C₃-C₆ 10 halocycloalkyl, halogen, CN, NO₂, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, C₁-C₄ alkylthio, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, C₁-C₄ alkylamino, C₂-C₈ dialkylamino, C₃-C₆ cycloalkylamino, C₃-C₆ (alkyl)cycloalkylamino, C₂-C₄ 15 alkylcarbonyl, C₂-C₆ alkoxy carbonyl, C₂-C₆ alkylaminocarbonyl, C₃-C₈ dialkylaminocarbonyl or C₃-C₆ trialkylsilyl;

15 R³ is H, C₁-C₄ alkyl, C₂-C₄ alkylcarbonyl or C₂-C₆ alkoxy carbonyl;

X is N or CR⁴;

R⁴ is H or R²;

R⁵ is C₁-C₄ alkyl; and

n is 0 to 3, provided when X is CH then n is at least 1.

20 2. A compound of Claim 1 wherein R¹ is H, C₁-C₄ alkyl or C₁-C₄ haloalkyl; and each R² is independently C₁-C₄ alkyl, C₁-C₄ haloalkyl, halogen or CN.

3. A compound of Claim 1 wherein n is 1 to 3.

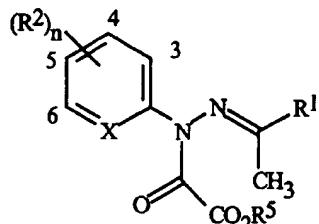
4. A compound of Claim 2 wherein R¹ is CF₃; each R² is independently Cl or Br, and one R² is at the 3-position; R³ is H; X is N or CR⁴; and R⁴ is H, Cl or Br.

25 5. A compound of Claim 2 wherein R¹ is CF₃; one R² is at the 4-position and is CN, and if an R² is present at the 5-position, it is F; R³ is H; and X is CH.

6. A compound of Claim 2 wherein X is N.

7. A method of preparing a compound of Formula I according to Claim 1 comprising

(1) treating a compound of Formula 6



6

wherein R⁵ is C₁-C₄ alkyl;

with a base; and when R^3 is C_1 - C_4 alkyl, C_2 - C_4 alkylcarbonyl or C_2 - C_6 alkoxy carbonyl,

5 (2) reacting with an alkylating or acylating agent suitable for substituting an R^3 for an alkoxide counterion to form a compound of Formula I.

8. The method of Claim 7 wherein step (1) comprises treating the compound of Formula 6 with a quaternary ammonium fluoride salt.

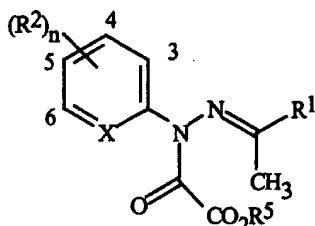
9. The method of Claim 7 wherein R¹ is H, C₁-C₄ alkyl or C₁-C₄ haloalkyl; and
10 each R² is independently C₁-C₄ alkyl, C₁-C₄ haloalkyl, halogen or CN.

10. The method of Claim 9 wherein R^1 is CF_3 ; each R^2 is independently Cl or Br, and one R^2 is at the 3-position; and R^3 is H.

11. The method of Claim 9 wherein R^1 is CF_3 ; one R^2 is at the 4-position and is CN , and if an R^2 is present at the 5-position, it is F ; R^3 is H ; and X is CH .

15 12. The method of Claim 7 wherein X is N.

13. A compound of Formula 6



6

wherein

20 R¹ is H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, C₁-C₆ haloalkyl, C₂-C₆ haloalkenyl, C₂-C₆ haloalkynyl or C₃-C₆ halocycloalkyl; each R² is independently C₁-C₄ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₆ cycloalkyl, C₁-C₄ haloalkyl, C₂-C₄ haloalkenyl, C₂-C₄ haloalkynyl, C₃-C₆ halocycloalkyl, halogen, CN, NO₂, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, C₁-C₄ alkylthio, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, C₁-C₄ alkylamino, C₂-C₈

dialkylamino, C₃-C₆ cycloalkylamino, C₃-C₆ (alkyl)cycloalkylamino, C₂-C₄ alkylcarbonyl, C₂-C₆ alkoxy carbonyl, C₂-C₆ alkylaminocarbonyl, C₃-C₈ dialkylaminocarbonyl or C₃-C₆ trialkylsilyl;

X is N or CR⁴;

5 R⁴ is H or R²;

R⁵ is C₁-C₄ alkyl; and

n is 0 to 3, provided when X is CH then n is at least 1.

14. A compound of Claim 13 wherein R¹ is H, C₁-C₄ alkyl or C₁-C₄ haloalkyl; and each R² is independently C₁-C₄ alkyl, C₁-C₄ haloalkyl, halogen or CN.

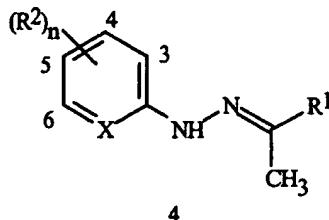
10 15. A compound of Claim 13 wherein n is 1 to 3.

16. A compound of Claim 14 wherein R¹ is CF₃; each R² is independently Cl or Br, and one R² is at the 3-position; X is N or CR⁴; and R⁴ is H, Cl or Br.

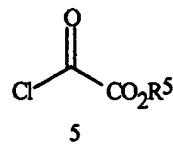
17. A compound of Claim 14 wherein R¹ is CF₃; one R² is at the 4-position and is CN, and if an R² is present at the 5-position, it is F; and X is CH.

15 18. A compound of Claim 14 wherein X is N.

19. A method of preparing a compound of Formula 6 according to Claim 13 comprising treating in the presence of base a compound of Formula 4



with a compound of Formula 5



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wherein R⁵ is C₁-C₄ alkyl.

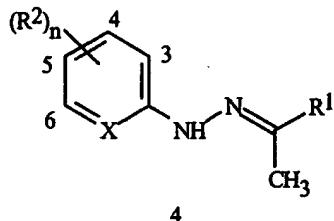
20. The method of Claim 19 wherein R¹ is H, C₁-C₄ alkyl or C₁-C₄ haloalkyl; and each R² is independently C₁-C₄ alkyl, C₁-C₄ haloalkyl, halogen or CN.

21. The method of Claim 20 wherein R¹ is CF₃; and each R² is independently Cl or Br, and one R² is at the 3-position.

22. The method of Claim 20 wherein R¹ is CF₃; one R² is at the 4-position and is CN, and if an R² is present at the 5-position, it is F; and X is CH.

23. The method of Claim 19 wherein X is N.

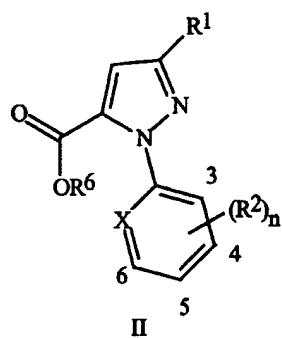
24. A compound of Formula 4



wherein R¹ is CF₃; each R² is independently Cl or Br, and one R² is at the 3-position; X is N or CR⁴; R⁴ is H or R²; and n is 0 to 3; provided that (i) when X is CH or CCl then n is at least 1 and (ii) when X is CCl, an R² at the 3-position is Cl and an R² is at the 5-position is Cl then n is at least 3.

25. A compound of Claim 24 wherein n is 1 to 3.

26. A method of preparing a compound of Formula II



10

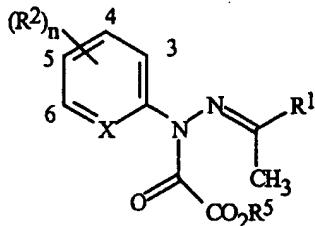
wherein R⁶ is H or C₁-C₄ alkyl; comprising

(3) treating a compound of Formula I of Claim 1 with acid; and when R⁶ is H,

(4) converting the product of (3) to form a compound of Formula II wherein R⁶ is H.

27. The method of Claim 26 wherein the compound of Formula I is prepared using a method comprising

(1) treating a compound of Formula 6



with a base; and when R³ is C₁-C₄ alkyl, C₂-C₄ alkylcarbonyl or C₂-C₆ alkoxy carbonyl, (2) reacting with an alkylating or acylating agent suitable for substituting an R³ for an alkoxide counterion.

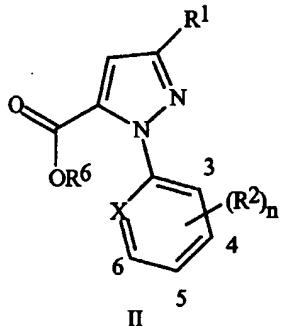
28. The method of Claim 26 wherein R¹ is H, C₁-C₄ alkyl or C₁-C₄ haloalkyl; and each R² is independently C₁-C₄ alkyl, C₁-C₄ haloalkyl, halogen or CN.

29. The method of Claim 28 wherein R¹ is CF₃; each R² is independently Cl or Br, and one R² is at the 3-position.

30. The method of Claim 28 wherein R¹ is CF₃; one R² is at the 4-position and is CN, and if an R² is present at the 5-position, it is F; and X is CH.

10 31. The method of Claim 26 wherein X is N.

32. A compound of Formula II



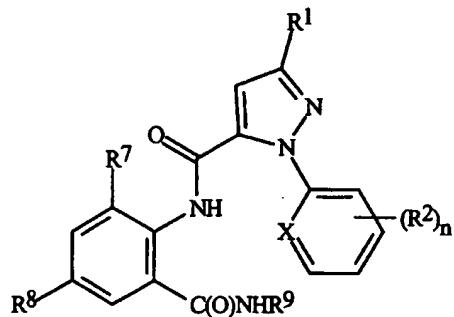
wherein R¹ is CF₃; each R² is independently Cl or Br, and one R² is at the 3-position; X is N or CR⁴; R⁴ is H, Cl or Br; R⁶ is H or C₁ to C₄ alkyl; and n is 0 to 3, provided when X is CH then n is at least 1.

15

33. A compound of Claim 32 wherein n is 1 to 3.

34. A compound of Claim 32 wherein X is N.

35. A method of preparing a compound of Formula III



wherin R¹ is H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, C₁-C₆ haloalkyl, C₂-C₆ haloalkenyl, C₂-C₆ haloalkynyl or C₃-C₆ halocycloalkyl;
 each R² is independently C₁-C₄ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₃-C₆ cycloalkyl, C₁-C₄ haloalkyl, C₂-C₄ haloalkenyl, C₂-C₄ haloalkynyl, C₃-C₆ halocycloalkyl, halogen, CN, NO₂, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, C₁-C₄ alkylthio, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, C₁-C₄ alkylamino, C₂-C₈ dialkylamino, C₃-C₆ cycloalkylamino, C₃-C₆ (alkyl)cycloalkylamino, C₂-C₄ alkylcarbonyl, C₂-C₆ alkoxy carbonyl, C₂-C₆ alkylaminocarbonyl, C₃-C₈ dialkylaminocarbonyl or C₃-C₆ trialkylsilyl;

10 X is N or CR⁴;

R⁴ is H, Cl or Br;

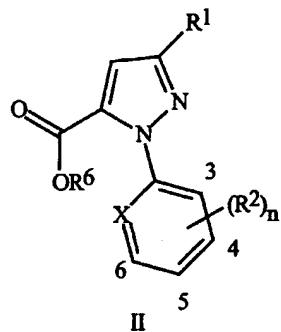
R⁷ is CH₃, Cl or Br;

R⁸ is F, Cl, Br, I or CF₃;

R⁹ is C₁-C₄ alkyl and

15 n is 0 to 3, provided when X is CH then n is at least 1;

using a compound of Formula II



wherein R⁶ is H; characterized by:

preparing said compound of Formula II by the method of Claim 26.

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(71) Applicant (for all designated States except US): E.I. DU PONT DE NEMOURS AND COMPANY [US/US]; 1007 Market Street, Wilmington, DE 19898 (US).

(72) Inventors; and

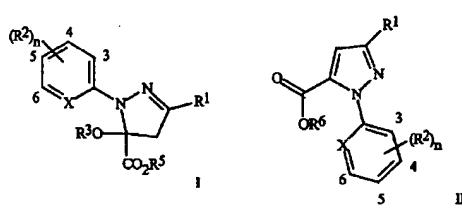
(75) Inventors/Applicants (for US only): ANNIS, Gary, David [US/US]; 13 Franklin Road, Landenberg, PA 19350 (US). LAHM, George, Philip [US/US]; 148 Fairhill Drive, Wilmington, DE 19808 (US). SELBY, Thomas, Paul [US/US]; 116 Hunter Court, Wilmington, DE 19808 (US). STEVENSON, Thomas, Martin [US/US]; 103 Iroquois Court, Newark, DE 19702 (US).

(74) Agent: HEISER, David, E.; E.I. du Pont de Nemours and Company, Legal Patent Records Center, 4417 Lancaster Pike, Wilmington, DE 19805 (US).

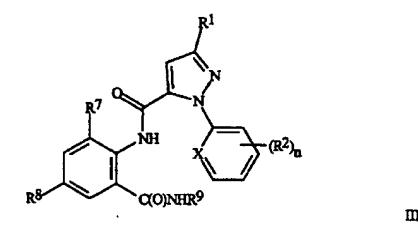
(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG,

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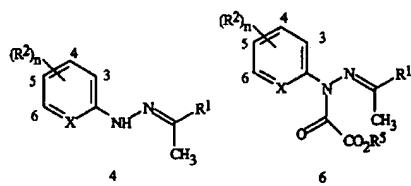
(54) Title: SUBSTITUTED 1H-DIHYDROPYRAZOLES, THEIR PREPARATION AND USE



(57) Abstract: This invention provides compounds of Formula (I), methods for their preparation and use for preparing compounds of Formula (II) wherein R₁?1, R₂?2, R₃?3, R₄?5, R₅?6, X and n are as defined in the disclosure. This invention also discloses preparation of compounds of Formula (III) wherein R₁?1, R₂?2, R₃?7, R₄?8, R₅?9 and n are as defined in the disclosure. This invention also pertains to certain compounds of Formula 4 and 6 used to prepare compounds of Formula (I), wherein R₁?1, R₂?2, R₃?5, X and n are as defined in the disclosure.



III



WO 03/016282 A3



SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) **Designated States (regional):** ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations of inventorship (Rule 4.17(iv)) for US only
- of inventorship (Rule 4.17(iv)) for US only
- of inventorship (Rule 4.17(iv)) for US only

Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB,

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INTERNATIONAL SEARCH REPORT

In national Application No
PCT/US 02/25612

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D401/04 A01N43/56 C07D231/16 C07D231/14 C07D213/77
C07D231/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	NL 9 202 078 A (RIJKSLANDBOUWHOGESCHOOL) 16 June 1994 (1994-06-16) the whole document ---	1-31
A	EP 0 333 131 A (HOECHST AG) 20 September 1989 (1989-09-20) claim 1; examples 71,191,911,1091 ---	26
P,A	WO 01 70671 A (DU PONT ; LAHM GEORGE P (US); MYERS BRIAN J (US); SELBY THOMAS P (U) 27 September 2001 (2001-09-27) cited in the application table 9 -----	1-31

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

* Special categories of cited documents :

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- "E" earlier document but published on or after the international filing date
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- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the International search

Date of mailing of the International search report

6 November 2002

18.03.2003

Name and mailing address of the ISA

Authorized officer

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

DE JONG B.S.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 02/25612

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-31

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-31

Compounds of formula I, the use of these compounds for the preparation of known compounds of formula II. The preparation of compounds of formula I and intermediates of formula 4 and 6, which are usefull for this preparation. The preparation of compounds of formula 4 and 6.

2. Claims: 32-35

Compounds of formula II and the use of these compounds for preparing compounds of formula III.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. onal Application No

PCT/US 02/25612

Patent document cited in search report		Publication date		Patent family member(s)	Publication date
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EP 0333131	A	20-09-1989	DE AT AU AU AU BR CA CN DD DE DK EP ES HU IL JP NZ PL PT SU US US ZA	3808896 A1 96273 T 3137389 A 634421 B2 8461491 A 8901210 A 1338071 A1 1035752 A 283538 A5 58905988 D1 128689 A 0333131 A1 2059596 T3 49785 A2 89620 A 1283274 A 228340 A 278285 A1 90041 A ,B 1836012 A3 5945541 A 5401700 A 8901960 A	28-09-1989 15-11-1993 21-09-1989 18-02-1993 14-11-1991 31-10-1989 20-02-1996 27-09-1989 17-10-1990 02-12-1993 18-09-1989 20-09-1989 16-11-1994 28-11-1989 29-12-1994 14-11-1989 27-08-1991 13-11-1989 10-11-1989 23-08-1993 31-08-1999 28-03-1995 25-10-1989
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